REMARKS

Claim Objections

Claims 2 and 8 are objected to for reciting non-elected subject matters. Claims 2 and 8 have been canceled.

Sequence Listing

Applicant hereby submits a Sequence Listing along with a Sequence Compliance Statement, a copy of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, and a formatted computer disk containing the Sequence Listing as a file D6392SEQ in text format.

Rejection Under 35 USC §112, 1st Paragraph

Claims 7-12 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is traversed.

The claims are drawn to a method of gene delivery that has increased targeting specificity to target cells and reduced transgene expression in non-target cells. The method involves the use of an adenoviral vector comprising (i) a targeting component that comprises a bi-specific molecule that binds to adenoviral knob protein and an angiotensin converting enzyme molecule expressed

on target cells, and (ii) a tissue-specific promoter that drives the expression of a transgene carried by said vector. The Examiner contends that when read in light of the specification, the sole purpose of the claimed method is to obtain therapeutic effects *in vivo*. Applicant respectfully disagrees.

Applicant submits that the subject matter and scope of the invention are defined by the claims. Claim 7 recites a method of gene delivery that has increased targeting specificity to target cells and reduced transgene expression in non-target cells. Claim 7 neither recites a method of gene therapy nor claims a method of obtaining therapeutic effects *in vivo*.

Applicant reiterates that the claims are simply drawn to a method of delivering gene to target tissue by adenoviral vector, and the claimed method fulfills a long-standing need in the art of gene therapy that desires an efficient gene delivery system (instant office action, page 6, first line). Hence, the present invention addresses one of the limitations of gene therapy, and "successful *in vivo* combination of transductional and transcriptional targeting approaches reported herein improves the prospects for gene therapy and provides an important proof-of principle for further vector development generally" (page 34, lines 17-21).

The utility of the claimed method would be readily apparent to one of ordinary skill in the art in view of the need for an efficient gene delivery system in the art. Moreover, the claimed gene delivery method is not only applicable to the delivery of therapeutic gene. One of ordinary skill in the art would readily recognize that the present invention is equally suitable and desirable for delivering marker gene to target tissue as shown herein.

Based on the data presented in the specification, Applicant submits that the claims on the gene delivery method have a reasonable correlation to the scope of enablement provided by the specification. The utility of combining transductional and transcriptional targeting approaches, for example for gene delivery to pulmonary vascular endothelium, was assessed in Example 5. A conjugate-based approach to target pulmonary endothelium *in vivo* via binding to angiotensin converting enzyme (ACE) was combined with the usage of the promoter for vascular endothelial growth factor type 1 receptor (flt-1 promoter) that has a high degree of activity in, and specificity for, endothelial cells. Initial studies were performed using the luciferase reporter gene system. The results indicate that such an adenoviral vector significantly enhances

transgene expression in target cells whereas transgene expression in non-target cells is significantly reduced (Figures 3-5; page 29, lines 6 to page 30, line 16; page 31, lines 16-21).

In view of these detailed description and data presented in the specification, Applicant submits that one of ordinary skill in the art can readily practice the instant invention of delivering a gene of interest to a target tissue without undue experimentation. Accordingly, Applicant respectfully requests that the rejection of claims 7-12 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection Under 35 USC §112, 2nd Paragraph

Claims 1-12 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is traversed.

Claims 1 and 7 are rejected for reciting "increased gene delivery" or "increased targeting specificity". The Examiner contends that the metes and bounds of the claims are not clearly determined due to lack of reference to which the enhanced activities are compared.

Claims 1 and 7 have been amended to recite the claimed adenoviral vector mediates increased gene delivery to target cells and reduces transgene expression in non-target cells as compared to

adenoviral vector without the targeting component and tissue-specific promoter disclosed herein. Such enhanced gene delivery and targeting specificity were clearly demonstrated in Example 5 and Figure 3. Applicant submits that the amended claims have clearly defined and claimed the metes and bounds of the subject matter. Accordingly, Applicant respectfully requests that the rejections of claims 1-12 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection Under 35 USC §102

Claims 1-2 are rejected under 35 USC §102(b) as anticipated by **Sosnowski** et al. (WO 98/40508). This rejection is respectfully traversed.

Claim 1 has been amended to recite an adenoviral vector comprising (i) a targeting component that comprises a bi-specific molecule that binds to adenoviral knob protein and an angiotensin converting enzyme molecule expressed on target cells, and (ii) a tissue-specific promoter that drives the expression of a transgene carried by said vector.

The Examiner contends that **Sosnowski** et al. disclose a tropism-modified adenoviral vector comprising (i) a targeting ligand

that binds to target cells, including targeting ligand which is conjugated to an antibody that binds an adenoviral knob protein, and (ii) a therapeutic gene under the control of a tissue-specific promoter. The Examiner further contends that **Sosnowski** et al. teach a number of cell surface molecules to which the targeting ligand can bind (pages 43-48). However, **Sosnowski** et al. do not teach or suggest using angiotensin converting enzyme molecule as a cell surface targeting molecule as claimed herein. Neither do **Sosnowski** et al. teach or suggest the cell surface target molecules listed on pages 43-48 have any resemblance or relationship with angiotensin converting enzyme molecule. Hence, **Sosnowski** et al. do not provide one of ordinary skill in the art with any reasonable basis to come up with the idea of using angiotensin converting enzyme as a cell surface targeting molecule.

The use of angiotensin converting enzyme as the cell surface targeting molecule is an essential feature for the present invention of adenovirus targeting. Since **Sosnowski** et al. do not teach or suggest each and every aspect of the present invention, **Sosnowski** et al. do not anticipate the present invention. Accordingly, Applicant respectfully requests that the rejection of claims 1-2 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-2 are rejected under 35 USC §102(e) as anticipated by **Sosnowski** et al. (U.S. Patent 6,613,563). This rejection is respectfully traversed.

Sosnowski et al. (U.S. Patent 6,613,563) disclose the same invention as **Sosnowski** et al. (WO 98/40508). Accordingly, as discussed above with regard to **Sosnowski** et al. (WO 98/40508), **Sosnowski** et al. (U.S. Patent 6,613,563) do not anticipate the present invention because **Sosnowski** et al. (U.S. Patent 6,613,563) do not teach or suggest each and every aspect of the present invention. Specifically, **Sosnowski** et al. (U.S. Patent 6,613,563) do not teach or suggest using angiotensin converting enzyme as a cell surface targeting molecule as claimed herein. In view of the above remarks, Applicant respectfully requests that the rejection of claims 1-2 under 35 U.S.C. §102(e) be withdrawn.

Rejection Under 35 USC §103(a)

Claims 1-6 are rejected under 35 USC §103(a) as being unpatentable over **Sosnowski** et al. (WO 98/40508) in view of **Muzykantov** et al. This rejection is respectfully traversed.

Sosnowski et al. (WO 98/40508) has been discussed above. The Examiner acknowledges that **Sosnowski** et al. do not

teach or suggest an adenoviral vector comprising a targeting component that binds to the angiotensin converting enzyme molecule as claimed herein. The Examiner contends, however, **Muzykantov** et al. disclose monoclonal antibody against angiotensin converting enzyme is a safe and specific carrier for drug targeting to pulmonary endothelium. Accordingly, the Examiner contends that it would have been obvious for one of ordinary skill in the art to modify the adenoviral vector of **Sosnowski** et al. to contain an anti-angiotensin converting enzyme antibody as a targeting agent.

Applicant submits that even though one of ordinary skill in the art may find it "obvious to try" the combination of **Sosnowski** et al. and **Muzykantov** et al., one does not have a reasonable expectation of success to carry out the presently claimed invention in light of the teaching of **Sosnowski** et al. and **Muzykantov** et al.

The present invention claims an adenoviral vector that mediates increased gene delivery to target cells and reduces transgene expression in non-target cells. The claimed adenoviral vector comprises two components, namely (i) a targeting component that comprises a bi-specific molecule that binds to

adenoviral knob protein and a angiotensin converting enzyme molecule expressed on target cells, and (ii) a tissue-specific promoter that drives the expression of a transgene carried by said vector. As it has been clearly shown in Example 5 and Figure 3 of the present specification, the increased gene delivery to target cells and reduced transgene expression in non-target cells are due to the presence of targeting component and tissue-specific promoter contained in the adenoviral vector.

In contrast, **Sosnowski** et al. do not provide an enabling disclosure on using tissue-specific promoter to reduce transgene expression in non-target cells as claimed herein. **Sosnowski** et al. only provide data and examples on adenoviral vectors carrying different targeting components. **Sosnowski** et al. do not present any data on using a tissue-specific promoter to reduce transgene expression in non-target cells. The need for actual experimentation on the use of tissue-specific promoter is highlighted by the prior art that teaches unsatisfactory level of expression as a drawback for tissue-specific promoter (instant office action, page 7, Sato et al.) Hence, absent any data that demonstrate the feasibility of using tissue-specific promoter to obtain a desired effect, **Sosnowski** et al. do not provide a person having ordinary skill in this art with the

requisite expectation of successfully using tissue-specific promoter to reduce transgene expression in non-target cells as claimed herein. Therefore, the invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claims 1-6 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed November 5, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Dec 9, 2003

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